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TECHNICAL REPORT 9102

OCCUPATIONAL HEALTH ISSUES RELATED TO NITROGLYCERIN EXPOSURE: REQUIREMENTS FOR POTECTIVE GLOVES AND DEVELOPMENT OF A BIOLOGICAL EXPOSURE INDEX

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JANUARY 1991

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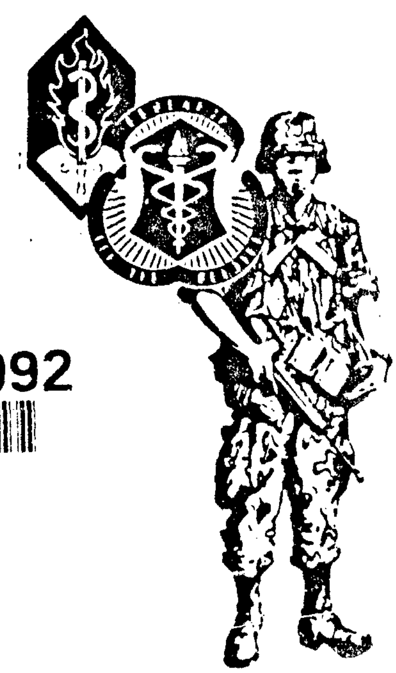

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Frederick, MD 21702-5012

Unclassified
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; unlimited distribution
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) 9102	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION U.S. Army Biomedical Research and Development Laboratory 6b. OFFICE SYMBOL (If applicable) SGRD-UBG-O	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21702-5010	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code)	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
0602787A	3M162787 A878	CA	

11. TITLE (Include Security Classification)
Occupational Health Issues Related to Nitroglycerin Exposure: Requirements for Protective Gloves and Development of a Biological Exposure Indes

12. PERSONAL AUTHOR(S)
W.G. Palmer, W.D. Burrows, and D.L. Parmer

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Technical	FROM Sep 88 TO Jan 91	January 1991	38

16. SUPPLEMENTARY NOTATION

17. COSATI CODES

FIELD	GROUP	SUB-GROUP
06	11	
23	04	

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
nitroglycerin, biological exposure index, toxicology, protective gloves, skin exposure

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Current practices with respect to protective gloves at Army ammunition plants that manufacture and incorporate nitroglycerin (NG) have been identified. The availability of alternative and presumably superior gloves has been examined. A literature review with respect to exposure indices suggests that it may be possible to monitor nitroglycerin exposure with NG and/or its metabolites in plasma and urine but that further research would be necessary before any of these options could be realized. Urinary NG metabolites represent the best prospect for biological monitoring since urine is easier to collect than plasma and is not complicated by factors such as the site of collection, which must be considered for blood. Before urine could be used for biological monitoring, human studies of the characteristics of metabolites and the time course of their appearance in urine during dermal exposure under controlled conditions would be necessary. Other studies must be performed to establish a biological exposure limit for the chosen metabolite(s).

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Winifred G. Palmer	22b. TELEPHONE (Include Area Code) 301-619-7207 22c. OFFICE SYMBOL SGRD-UBG

DD Form 1473, JUN 86 Previous editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
Unclassified

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SECTION I

OVERVIEW

The Command Surgeon, U.S. Army Armament, Munitions and Chemical Command (USAMCCOM) requested that the U.S. Army Medical Research and Development Command develop a research plan to meet the needs of personnel exposed to nitroglycerin (NG)(1). The request was motivated by a concern that despite continued improvements in reducing air concentrations of NG and related nitrate esters, exposure via the dermal route was continuing. A specific concern was associated with workers loading powder bags at Indiana Army Ammunition Plant. The following priorities of effort were recommended:

a. Develop control methods to prevent any exposure to these compounds which may cause adverse health effects. Include improvements in personal protective equipment; i.e. gloves, shoes, clothing and engineering control recommendations.

b. Develop a practical, accurate method to assess total worker exposure to nitrate esters while working with double and triple-based propellants.

c. Assess the potential effects on reproduction, teratogenicity, mutagenicity and carcinogenicity of these nitrate esters.

This report addresses recommendations a and b above. Sections II and III represent an investigation into the issues involved in developing improved methods for hand protection and evaluation of dermal exposure through the development of a Biological Exposure Index (BEI).

SECTION II

OCCUPATIONAL HEALTH ISSUES RELATED TO NITROGLYCERIN EXPOSURE: PROTECTIVE GLOVES

INTRODUCTION

The present discussion addresses gloves worn for protection in the manufacture of nitroglycerin (NG) and NG products. Tasks undertaken for this study were to identify current practices with respect to protective gloves at Army ammunition plants manufacturing NG, to document existing health problems associated with NG dermal exposure, and to seek alternative and presumably superior gloves for handling NG-containing materials.

INDUSTRIAL HYGIENE PRACTICES

Radford Army Ammunition Plant (RAAP)

The industrial hygiene protocol at RAAP since 1973 provides for three lockers for each NG worker (3). At the beginning of each shift, the worker hangs his clothing in the first locker and puts on a complete fresh uniform, including underwear, from the second. At the end of the shift, all used (contaminated) clothing is placed in the third locker to be laundered, and the worker showers before dressing in street clothing. The uniform includes Nomex[R] coveralls and gloves appropriate to the task as noted below. Respirators are worn in the roll powder building where double-base propellant (nitrocellulose plus NG) is manufactured.

Four basic glove types are in service at RAAP NG facilities, depending on the duty: surgeon's gloves, leather-palm gloves, cotton gloves and plastic-coated cotton gloves. Nitroglycerin and diethyleneglycol dinitrate (DEGDN) will eventually penetrate all of them. The Technical Analytical Group at RAAP has developed a simple test for NG penetration (4). A 5-cm disk cut from the palm of a glove is placed outer-side-down on a 5-cm disk of sheet propellant; on top of the glove is placed a 5-cm disk of sheet woodpulp and a 1-kg weight, also 5 cm in diameter. The assembly is placed on a steam oven at about 70 $^{\circ}C$ for 7 hours, after which the woodpulp disk is macerated, extracted with methanol, and analyzed for NG by liquid chromatography. Gloves are approved only if penetration to the woodpulp disk does not exceed 0.1 mg/cm^2; results of some initial tests are presented in Table 1. An older method is occasionally used: palm and finger sections of gloves actually worn during performance of a task for a specified time period are extracted and tested for NG penetration. Cotton gloves are changed every hour (4). The procedure whereby gloves are discarded when they develop a "wet feel" is outdated. An alternative test procedure, ASTM Test for Resistance of Protective Clothing Materials to Permeation by Hazardous Liquid Chemicals (F 739-85), utilizes a two-chamber test cell with the liquid challenge chemical applied to the outside of a protective clothing sample and a collecting medium in contact with the inside (5). This procedure would present an unacceptable hazard in the case of NG, and it would be inappropriate for gloves used in handling propellant. Specific glove types used at RAAP and minimum change frequencies for all RAAP operations are presented in Appendix A.

TABLE 1. Test Results with RAAP Test Method(4)[a]

Glove type	Manufacturer	NG penetration, mg/cm^2	Remarks
Nitrile, LA-111-EB-F1	North	ND[b]	approved
Malaysia	unknown	0.095	approved
P/N 796 nitrile w/cotton flock	Best	ND	approved
Neoprene No. 3214	Best	0.011	approved
Cotton, L-6-2493 fawn color	made in Thailand	0.140	not approved
G322EKJ, tan color	Stauffer	0.081	approved
L6322EKJ	Stauffer	0.030	approved
MC-41-13-560	Plasco	0.051	approved
Style 312	Tri-State Physic.	0.19	not approved
Cotton dipped in plastic, seamless	Not specified	0.022	approved
RN brown leather palm lines w/napped cotton	Not specified	0.038	approved
Worknit HD 05/3729L brown plastic-coated cloth	Norton	0.052	approved
#1A1 light weight plastic-coated cloth	Plasco	0.141	not approved
White cotton, napped inside	Not specified	0.269	not approved

a. 24 April 1984
b. ND = none detected

Indiana Army Ammunition Plant (INAAP)

In 1989 the M203 line, which produced 155 mm howitzer charges, was the only propellant line at INAAP involving materials that contain NG. Single base stick propellant incorporating 18 percent NG, is received from RAAP in shipping boxes. The propellant is weighed out and tied up into 27-lb bundles. The bundles are then wrapped tightly in a cloth jacket with a lead foil liner, fitted into combustible casings with igniters and sealed in individual storage containers. Gloves are worn for all operations. For the weighing operation, which involves the most intimate contact with the propellant, two pairs of

cotton gloves are worn; the outer pair (showing some graphite soiling) is discarded every 2 hours (6). Tying on liner jackets requires finger dexterity, and workers were observed to have cut off the thumb and first one or two fingers of the gloves at the first joint. There is some incidental contact of bare fingers with the propellant. Workers wear caps and one-piece coveralls treated with fire-retardant; these are changed every day. Respirators were not worn.

HEALTH PROBLEMS RELATED TO NG EXPOSURE

RAAP

Health problems among munitions plant workers resulting from dermal exposure to NG have been documented throughout most of this century. All the classical symptoms (headache, nausea, blurred vision) were commonly observed at RAAP, sole producer of NG for the U.S. Army, before modern industrial hygiene was practiced (7). At present, these symptoms are observed only occasionally in new or unusually sensitive employees, which may attest to the efficacy of masks and protective garments. Indeed, RAAP health and safety personnel do not perceive that there is a problem with respect to dermal exposure through gloves, provided that the glove protocol is rigorously followed. (Reports of headaches and nausea are not necessarily symptomatic of NG exposure, since ELBA solvent, a mixture of ethyl lactate and butyl acetate, causes the same complaints in many workers.)

INAAP

The circumstances that led to INAAP's original concern for NG exposure appear no longer to apply, due to a product change (6). Through the mid-1980's, the 155 mm howitzer round was propelled by a bag powder charge. The powder consisted of double-base propellant grains coated with graphite, and loading of powder bags was a very dusty operation. The dust filtered through clothing and adhered to the skin of the loaders. Since the dust contained almost as much NG as the propellant, the loaders were considered at risk of skin exposure to NG. As noted above, the present M203 charge uses stick propellant in a combustible case rather than a bag, the graphite is incorporated into the propellant, and no dust is generated. It is understood that there are occasional complaints of headaches among loaders, but the source of exposure, if NG is indeed the cause, is undefined.

AVAILABILITY OF ALTERNATIVE SAFETY GLOVES

The second task in this project was to inquire into the availability of alternative gloves which would be more impervious to NG while allowing the user sufficient dexterity to perform such operations as handling individual roll powder grains. It also was considered important that the glove material not allow build-up of static electricity (although workers in sensitive areas are electrically grounded, and static build-up has not been a problem).

A list of manufacturers/distributors of chemical safety gloves was compiled using the Thomas Register, RAAP's current suppliers, and sources identified therefrom. Telephone contact with technical service departments

elicited a nearly uniform response: companies were willing to help identify an existing glove most suitable for our purposes and to conduct the necessary tests, but were not prepared to initiate a developmental effort to make a glove impervious to NG from new materials. One manufacturer (Pioneer) noted that new polymeric materials are available, but that it would be more than a year before they would be able to address our problem. The impression gained from conversation with manufacturers is that the capability exists to develop new gloves to meet the Army's needs, but it will probably be identified only through responses to a Request for Proposal. Telephone contacts with safety glove manufacturers with developmental capabilities are summarized below.

Best Manufacturing Co., Menlo, GA, 404-862-2302

The chief chemist was not interested in working with NG products, but the marketing director would be willing to discuss it in the future.

Pioneer Industrial Products, Willard, OH, 414-993-2211

The chief chemist and chief for research and development noted that new polymeric materials are available, but that it would be more than a year before developmental work could be contemplated.

Edmont Wilson, Coshocton, OH, 614-622-4311

The chief for research and development suggested that the best protection may be achieved by wearing laminated polyvinyl acetate or polyethylene gloves (such as worn by food handlers) under nitrile gloves.

North Hand Protection, Charleston, SC, 803-554-0660

Butyl rubber gloves were recommended.

Chem-Fab Corporation, Merrimac, NH, 603-424-9000

Chem-Fab manufactures protective suits for various industries, but procures gloves elsewhere. They noted that experience with Teflon gloves had been less than satisfactory, largely because of material stiffness.

SUMMARY AND RECOMMENDATIONS

The RAAP has a detailed protocol for the use of protective gloves when handling materials that contain NG, as well as a test procedure which measures the rate of penetration of NG through the gloves. Assuming that the protocol is followed, these gloves, the selection of which depends upon the operation, should provide reasonable protection against NG skin exposure. At INAAP the potential for exposure to NG is presently low compared with RAAP, and industrial hygiene protocols are accordingly less rigorous. Again, double thickness gloves appear to provide protection against NG skin exposure. However, some operations require such dexterity that workers have cut some of the fingers from the gloves, and there is incidental exposure to NG-containing propellant.

Although there are manufacturers of safety equipment potentially capable of developing new gloves that could provide better protection against exposure to NG, it would be premature to initiate such development in the absence of evidence that NG workers are at risk of skin exposure through gloves.

REFERENCES, SECTION II

1. 9th End, HQ, USAMRDC, SGRD-PLC, undated, to letter, HQ, USAMCCOM, AMSMC-SG, 29 Dec 1986, subject: Occupational Health Issues Related to Nitroglycerin Exposure.

2. 6th End, HQ, USAMCCOM, AMSMC-SG, 4 Jan 1988, to letter, HQ, USAMCCOM, AMSMC-SG, 29 Dec 1986, subject: Occupational Health Issues Related to Nitroglycerin Exposure.

3. Topper, T. Hercules, Inc. Personal communication, April 1989 (updated January 1991).

4. Bowen, S. Memorandum, Hercules, Inc., Radford Army Ammunition Plant, 24 April 1984, subject: NG Penetration of Gloves.

5. American Society for Testing and Materials. 1983. Performance Standards for Textile Fabrics. Philadelphia.

6. Bynum, R. ICI Americas, Inc. Personal communication, June 1989.

7. Salinas, A., MD. Hercules, Inc. Personal communication, April 1989.

SECTION III

DEVELOPMENT OF A BIOLOGICAL EXPOSURE INDEX FOR NITROGLYCERIN

INTRODUCTION

Nitroglycerin is an explosive used in dynamite, gunpowder, and propellants. It is in wide use in medicine for the treatment of angina. As a potent vasodilator, its short-term effects include throbbing headache, increased pulse rate, decreased blood pressure, palpitations, nausea, and vomiting. Although headaches are a sensitive indicator of exposure among persons new to dynamite work, NG tolerance usually develops within 2 to 4 days. Tolerance is short-lived and is generally lost after brief periods away from the work place. Withdrawal from long-term exposure has been associated with angina pectoris and sudden death in workers. Although the cause of the latter phenomenon is not established, it is thought to result from a compensatory vasoconstriction which continues after exposure to NG discontinues (10).

Two epidemiological studies of separate populations of Swedish dynamite workers suggested an association between long-term dynamite work and excess mortality from chronic cardiocerebrovascular disease (23). Records of exposures to airborne NG were not available during those studies; and thus, an association between specific exposure levels and development of disease could not be made. More recently, a mortality study of workers exposed to NG between 1949-1977 at RAAP, a munitions plant in Virginia, was conducted by the National Institute for Occupation Safety and Health (NIOSH). In this work, a significant excess of ischemic heart disease was found in NG-exposed workers in the age group 40 to 49 years (43).

Nitroglycerin is readily absorbed by ingestion, inhalation, and through the skin. When both inhalation and dermal exposures occur, dermal contact is generally thought to make a greater contribution to the total amount of NG absorbed by the body (10, 17). Natural and synthetic rubber are not impervious to NG and protective clothes in use today are only partially effective in preventing exposure (10, 17). Thus, the potential for absorption of NG through the skin exists in industries where this substance is used.

At present, there are no means of monitoring dermal exposure to NG in the workplace. This information is vital for relating information derived from health effects studies to worker exposure and for establishing realistic exposure limits. The object of this paper is to examine the pharmacokinetics of NG to determine whether levels of NG or its metabolites in body fluids (i.e., expired air, plasma, or urine) could serve as biological exposure indices (BEI) for NG.

CHEMISTRY

Little was known about the pharmacokinetics of NG before 1965. After that time, with the use of thin-layer chromatography, colorimetry, and radioisotope tracers, information about the metabolism and distribution of this drug began to emerge. In 1973, Rosseel and Bogaert (44) developed the first assay for NG

capable of detecting the exceedingly low (ng/ml) concentrations present in plasma of exposed persons. This method coupled benzene extraction with gas chromatography using an electron capture detector (GC/ECD) and achieved a sensitivity of 0.5 ng/ml for NG (44). Subsequent modifications of this procedure, including the introduction of glass capillary columns, increased the sensitivity, specificity, and resolution of NG metabolites in urine, plasma, and body tissues (18, 30, 45, 47, 49, 52). Methods employing other techniques such as high-pressure liquid chromatography (51) and gas chromatography/mass spectroscopy (47) have been reported. However, because of its accessibility and ease of operation, GC/ECD has been the most commonly used analytical method in recent years.

Nitroglycerin is unstable in biological samples and is subject to microbial degradation (29). Thus, considerable care must be taken in collection and storage of biological materials. More details about problems of handling and storage, and the development of analytic procedures can be found in a review by Curry and Aburawi (11).

ENZYMATIC DEGRADATION

Nitroglycerin is sequentially denitrated to the metabolites glyceryl dinitrate (GDN) and glyceryl mononitrate (GMN) by the enzyme organic nitrate reductase (37). This glutathione-dependent enzyme reaction occurs predominantly in the liver; but it has also been found in the arteries, veins, muscle, lung tissue, and red blood cells (14, 15, 36). The half-life of NG is about 1 minute in isolated perfused rat liver; while in blood, denitration is relatively slow with a half-life of about 20 minutes at an optimum temperature of 50 to 57^{o}C (36). With time, the di- and monoglycerylnitrates are further degraded by other enzyme systems to glycerol and CO_2. The glucuronides of NG, GDN, and GMN are present in urine.

Short and Dacre (46) found differences in the relative quantities of 1,2-GDN to 1,3-GDN produced by liver homogenates from different species. The ratio was 0.3 for monkey, 0.4 for rabbit, dog, and human, 1.4 for rat, and 2.4 for mouse. As with other liver enzymes, organic nitrate reductase is induced by phenobarbital and inhibited by SKF 525A. Bogaert showed that, following treatment with NG, plasma organic nitrate levels decrease in animals pretreated with phenobarbital and increase in those pretreated with SKF 525A (9). The converse is true for urinary excretion of NG metabolites (7).

ABSORPTION AND METABOLISM

Plasma NG Levels

Many studies of the absorption, metabolism, and excretion of NG have been performed in man and laboratory animals. Although there are some interspecies differences, the pharmacokinetics and distribution patterns of NG and its metabolites are similar in most species. NG is readily absorbed following dermal, intravenous (i.v.), sublingual, and oral exposure. Maximum NG levels are reached in the blood shortly after i.v. and sublingual administration. Its rapid metabolism, elimination, and extensive tissue distribution result in rapid clearance of NG from the blood.

Peak plasma concentrations of NG occur within 2 to 6 minutes after sublingual administration to humans (2, 5, 17, 50). The maximum concentrations attained are quite low and vary between 1 ng/ml and 2.3 ng/ml for doses of 0.3 mg to 0.6 mg, respectively (2, 50). The disappearance of NG from plasma follows first order kinetics (53). According to Gjesdal, the half-life is independent of the maximum NG concentration achieved in plasma (17). Typical plasma half-lifes following sublingual administration or injection into the bloodstream are shown in Table 2.

TABLE 2

PLASMA NG HALF-LIFES

Species	Route of Administration	Half-life (minutes)	Reference
Rat	intracardial	4.2	53
Man	i.v.	3.0	34
Man	sublingual	3.0	17
Man	sublingual	4.4	2

In 1972, Needleman (38) determined blood clearance rates during the first 2 minutes after i.v. injection of radiolabeled NG. Blood clearance was extremely rapid immediately after dosing. The clearance was biphasic; an initial fall in NG levels occurred with a half-life of about 10 to 14 seconds during the first 30 seconds. Clearance proceeded with a half-life of about 1 minute between 30 and 120 seconds after administration. By 1 minute, about 80 percent of the parent nitrate was cleareo from the blood. By 10 minutes, only 5 percent of the radioactivity present at 10 seconds remained; and by 15 minutes, no detectable NG was present in the blood.

DiCarlo et al. (12) and Hodgson and Lee (22) showed that when radiolabeled NG is administered to rats, the radioactivity in the blood represents only a small fraction of the total administered dose. McNiff (34) estimated that only about 1.3 percent of the total body load of NG is found in the plasma. Its apparent volume of distribution (V_d) is high, indicating that NG is extensively distributed in the body. In the rat, the V_d following intracardial injection was calculated to be 3.1 liter/kg which is not significantly different from the V_d of ?.7 liter/kg resulting from administration by gavage (53). Volumes of distribution of 3.3 liter/kg (34) and 2.6 liter/kg (2) were estimated in humans following i.v. infusion and sublingual administration, respectively.

Following administration of radiolabeled NG, radioactivity can be detected in many tissues and organs (12, 22). Although the relative quantities of radioactivity in different organs vary with the species, the highest concentrations are generally found in the liver. The levels of radioactivity

decline rapidly in most organs but may remain elevated in the liver for 24 hours (22).

Bogaert et al. (8, 9) reported that plasma NG levels declined immediately after i.v. injection in the rabbit and dog. Plasma nitrate levels then gradually increased towards a maximum at 10 to 20 minutes after administration. The early profile of NG in plasma was attributed to the rapid uptake of NG by different organs, especially the liver, with a subsequent release from the tissues back into the bloodstream. In support of this premise, Bogaert showed that tissue (liver, kidney, heart, lung, striated muscle, and fat) levels were highest at 2 minutes after i.v. injection when plasma nitrate levels were low, while the converse was true at 20 minutes. While Bogaert thought that the nitrate in plasma at 10 to 20 minutes after injection was unchanged NG, later investigators (47, 51), using more refined techniques, demonstrated that NG disappears rapidly from plasma; the nitrates appearing after the initial decline of NG are, for the most part, NG metabolites.

In contrast to i.v. administration, Bogaert et al. noted that, after gastric intubation of NG, organic nitrate levels increased slowly in plasma and reached a maximum in 35 minutes (9). Again, the organic nitrates which Bogaert observed were probably NG metabolites since later studies established that oral administration of NG results in sustained levels of NG metabolites with little of the parent compound in the blood (38, 39).

To account for the paucity of unchanged NG in the bloodstream following oral administration, Needleman et al. postulated that NG is extensively metabolized to the di- and monoglyceryl nitrates during its first passage through the liver with little or none of the NG being released from the liver as the intact parent compound (38). Later studies showed that the liver cannot be responsible for all NG metabolism and that substantial metabolism occurs in other tissues (11).

Metabolites in Plasma

Nitroglycerin metabolites are cleared slowly from plasma in accordance with first-order kinetics. Mizuguchi et al. (35) measured the rate of disappearance of radioactive materials from plasma following i.v. injection of ^{14}C-NG and found that labeled metabolites disappear from rat plasma with a half-life of 2.13 hours. Using similar experimental conditions, Needleman et al. (38) found that the half-life of NG metabolites is almost 4 hours.

Needleman et al. (38) found that metabolites appeared in the blood within 5 minutes after administration of radioactive NG to rats by gavage. At that time, unchanged plasma NG represented 2 percent or less of the total quantity of the administered radiolabel. The relative concentrations of NG and its metabolites in plasma for the first 4 hours after NG administration are shown in Table 3.

TABLE 3

PLASMA METABOLITE LEVELS IN RATS TREATED ORALLY WITH ^{14}C-NG

Time (min)	NG (cpm)	Metabolites (cpm)
5	96	5940
30	192	6609
60	158	6956
120	126	7169
240	0	5488

Data from Needleman et al., (38)

In 1986, Noonan et al. reported that elimination half-lifes for dinitrate metabolites are approximately twenty-fold longer than the 2 to 3-minute half-life of the parent compound (40). Woodward et al. (51) found that the dinitrate isomers reach a peak at 10 minutes after sublingual exposure to 600 μg NG and decline very slowly thereafter. Substantial levels were present in plasma at 30 minutes after exposure. Nitroglycerin reached a peak within 5 or 6 minutes after exposure and declined rapidly to almost nondetectable levels within 20 minutes.

In 1987, Soufi et al. (47) examined organic nitrates in the plasma of four subjects who received NG (300 μg) by i.v. infusion for 30 minutes. Blood was collected at 1, 15, 30, and 45 minutes and organic nitrates were examined by GC/ECD. 1,2-GDN, but not 1,3-GDN, was detected in plasma. Nitroglycerin was not detectable at 45 minutes.

In contrast, Langseth-Manrique and Bredesen (30) detected 1,3-GDN in plasma from 2 cardiac patients who received i.v. infusions of NG for a period of 2 days. Plasma samples were obtained periodically throughout the infusion and examined by capillary GC/ECD. For the first 24 hours of the infusion, there were approximately equal quantities of 1,3-GDN and NG and about six times more 1,2-GDN. The six-fold difference between 1,2-GDN and 1,3-GDN was maintained throughout the 48-hour infusion period.

Noonan and Benet (39) showed that the relative proportions of NG metabolites vary with the route of administration in humans. The ratios of 1,2-GDN to 1,3-GDN were 7.36, 4.60, 3.86, and 1.99 for i.v., sublingual, topical, and oral doses, respectively. The ratios were constant for 3 hours after administration and were significantly different for oral and i.v. exposures. In this study, 6.5 mg NG in drinking water was administered to four men. Two others received 0.4 mg sublingually, and a topical ointment containing 20 mg NG was spread evenly over a 200 cm^2 area on the chest of four other subjects for 5 hours. Nitroglycerin was administered by i.v. infusion (10, 20 and 40 μg/min) to four subjects. The elimination half-lifes for each exposure route are shown in Table 4.

TABLE 4

PLASMA HALF-LIFES OF NG METABOLITES

Route of Administration	Half-life (minutes ± S.D.) 1,2-GDN	1,3-GDN
Oral	44.1 ± 8.3	42.6 ± 10.6
I.V. Infusion	33.2 ± 6.5	57.2 ± 30.0
Transdermal	35.8 ± 10.3	67.3 ± 11.7
Sublingual	36.5 ± 6.9	43.8 ± 12.0

Data from Noonan and Benet (39)

Overall, there were no significant differences between the half-lifes for 1,2-GDN and 1,3-GDN or between the half-lifes observed after different routes of administration. The relative concentration of 1,3-GDN was greater after passage across dermal and sublingual membranes than after i.v. injection. To explain this, Noonan presented the hypothesis that the specificities of enzymes in the sublingual mucosa and viable stratum corneum of skin differ from those in other tissues. Whereas systemically administered NG is metabolized preferentially to the 1,2-isomer, metabolism in the skin and sublingual mucosa are more specific for 1,3-GDN.

Dilley reported that plasma half-lifes of 1,2-GDN and 1,3-GDN ranged from 22 to 34 minutes and 24 to 45 minutes, respectively, in 4 dogs injected i.v. with ^{3}H-NG (13). Glyceryl mononitrate levels were relatively stable during the 2-hour post-injection observation period. Repeated exposure to NG increased the plasma half-lifes of the metabolites. Tritiated-nitroglycerin was injected i.v. before and 1 day after a 10-day period of exposure to NG by inhalation. The biological half-lifes of 1,2-GDN and 1,3-GDN were 25.3 and 49.8 minutes before, and 35.3 and 68.3 minutes after repeated exposure to NG vapor. Idzu et al. (26) similarly noted that repeated percutaneous exposure lengthened plasma clearance times in rats (see below).

Elimination

Nitroglycerin metabolites are excreted in urine, feces, and as CO_2 in expired air. Kikukawa and Kagitani (28) found that about 97 percent of the total dose of radiolabeled NG administered by i.v. injection to rats was excreted in 48 hours; 54 percent was found in urine, 33 percent was expired, and 10 percent was present in feces. Hodgson and Lee obtained similar results after oral administration of radioactive NG to rats (22). At 4 hours, 21 percent, 2.3 percent, and 19.8 percent of the administered dose was found in the urine, feces and exhaled air, respectively. Lee et al. (32) showed that the fraction excreted by different routes varies with the species. While mice and rats excreted substantial amounts in both the urine and expired air, urine was the main route of elimination for the rabbit, monkey, and dog.

When DiCarlo et al. (12) treated rats with a single gavage dose of ^{14}C-NG, more than half the radiolabel was removed from the gastrointestinal tract

within 30 minutes. At this time, 6.4 percent of the total dose was present in blood and 7 percent was in the liver. After 4 hours, 2.5 percent remained in the liver. Of the total radiolabel in the body, 2.9 percent, 6.1 percent, 15.5 percent, and 21 percent appeared in the urine at 0.5, 1, 2, and 4 hours, respectively. At 4 hours, only 2 percent of the label was present in feces while the amount present as CO_2 exhaled was approximately the same as that in urine.

Bogaert et al. (7) administered NG (1 mg/kg i.v.) to four rabbits and observed GMN and 1,3-GDN, but not 1,2-GDN, in urine within a few minutes after NG dosing.

DiCarlo et al. (12) found no unmetabolized NG in the urine of rats treated orally with ^{14}C-NG. Glycerol was the principal metabolite. In contrast to the findings of Bogaert (7), there was considerably more 1,2-GDN than 1,3-GDN in the urine. The relative amounts of the monoglycerides increased with time (Table 5).

TABLE 5

PERCENT OF ADMINISTERED NG PRESENT IN RAT URINE
WITH TIME AFTER DOSING

Metabolite	30 min	1 hr	2 hr	4 hr
1,2-GDN	0.40	0.10	0.87	1.29
1,3-GDN	0.11	0.04	0.43	0.51
1-GMN	0.20	0.25	2.05	2.41
2-GMN	0.23	0.16	1.62	1.88
glycerol	0.95	2.80	4.25	6.64

Data from DiCarlo et al. (12)

Needleman et al. (36) reported that 49 percent of the ^{14}C-NG administered to rats by subcutaneous injection was recovered in the urine within 24 hours. Of the total counts present in rat urine at 24 hours after treatment, 2.7 percent was NG, 4 percent was 1,3-GDN, 12 percent was 1,2-GDN, 65 percent was GMN, and the remainder was unidentified water-soluble compounds.

O'Rourke et al. (42) determined metabolite levels in urine collected at 6, 24, and 30 hours after oral administration of 20 mg NG to dogs. The 6-hour urine sample contained some intact NG, larger amounts of the two dinitroglycerins, and probably a mononitrate. After 24 hours, NG was no longer present in the urine, and by 30 hours, no nitrates were found.

Clearance of Individual Metabolites

Hodgson et al. (21) administered both isomers of ^{14}C-labeled GDN and GMN by gavage to rats. Of the administered doses, 20 percent of the GDNs and 20 percent of the 1-GMN, but only 7 percent of the 2-GMN, were recovered in expired air within 24 hours. About 50 percent of the administered doses of 1,2-GDN and 2-GMN, but only 25-30 percent of the administered 1,3-GDN and 1-GMN doses, appeared in 24-hour urine samples. The free GMNs, glucuronide conjuqates of GDN and GMN, glycerol and other polar metabolites were present in the urine of rats treated with isomers of GDN. Administration of the isomers of GMN resultea in the appearance of substantial amounts of unchanged GMN in urine as well as glycerol and other polar metabolites. No GMN-glucuronides were found. In a study with humans, Bogaert et al. (6) administered capsules containing either NG, 1,2-GDN, 1,3-GDN, or 1-GMN to 4 volunteers. (Capsules were given to avoid absorption through the buccal mucosa.) After administration of NG, GMN was excreted in the urine for 9 to 27 hours. Glyceryl mononitrate was the major metabolite found in urine after administration of the dinitrates. Administration of the mononitrate, led to the urinary excretion of GMN for 7 to 9 hours.

Laufen and Leitold (31) administered 1-GMN by i.v. infusion or by mouth to 10 healthy men. The average elimination half-lifes were 2.50 and 2.54 hours after i.v. and oral dosing, respectively. Twenty percent of the excreted GMN was in the conjugated form. The intersubject variances in pharmacokinetic parameters were much lower than normally seen with NG.

In a similar study, a single human volunteer was given 20 mg 1-GMN in drinking water and the quantity of 1-GMN in plasma was measured. Levels of 1-GMN peaked soon after administration and declined rapidly thereafter. It was not detectable 24 hours later (45). The terminal plasma half-life was calculated to be 3.6 hours.

TRANSDERMAL ABSORPTION

Glyceryl trinitrate and its metabolites may be found in plasma during dermal contact with NG. Depending on the dose and method of application, plasma NG frequently attains concentrations of 1 to 10 ng/ml during continuous transdermal administration in therapeutic regimens (11). In 1985, Curry and Aburawi (11) noted that NG is not detectable in plasma at doses below a threshold level (16). They conjectured that this is due, in part, to the processing of NG within skin cells. Thus, if low doses of NG are extensively metabolized during passage through the skin, the parent compound might not be detectable in plasma. Indeed, more recent work indicates that NG metabolism can occur within skin tissue. In human studies, Llcyd found that 1,2-GDN and 1,3-GDN appeared with time in NG-contaminated skin (33). The relative amounts of the dinitrates rapidly increased during the first 8 hours after skin contact with a concomitant rapid loss of NG. After that, the change occurred more slowly. The ratio of 1,2-GDN to 1,3-GDN varied between 1.5 and 2 during the first 38 hours after exposure.

In comparison with other routes of administration, there has been little work on the characteristics of NG metabolites following transdermal

absorption. In his limited study with two dogs, Dilley (13) found that 1,2-GDN, 1,3-GDN, and GMN, but virtually no NG, were present in blood during percutaneous administration of ^{3}H-NG. The plasma concentrations of NG metabolites increased erratically during the 5-hour transdermal exposure period. The profile of plasma metabolites was similar in monkeys treated under comparable conditions. However, in monkeys, NG appeared transiently in plasma at 4 hours after exposure began. In both dogs and monkeys, there was about twice as much 1,2-GDN as 1,3-GDN in plasma (13). The ratios of 1,2-GDN to 1,3-GDN reported by Dilley (13) and Lloyd (33) are consistent with the findings of Noonan who showed that the ratio of 1,2-GDN to 1,3-GDN is lower in plasma following topical administration compared to sublingual or i.v administration (39).

Idzu et al. (26) repeatedly administered ^{14}C-labeled NG percutaneously to rats for 1 week. The maximum level of radioactivity in plasma was attained 4 hours after administration. Within 3 to 4 days, the level of radioactivity in plasma attained a steady state. The major metabolites in urine were GMN and 1,2-GDN glucuronide. These metabolites were present in the same relative concentrations in urine after oral and i.v. administration.

The surface area of the skin to which NG is applied may have a major influence on rates of transdermal absorption. In studies with the Rhesus monkey, Noonan and Wester (41) showed that increasing the exposed surface from 2 cm^2 to 50 cm^2, while keeping the total amount applied constant, increased NG absorption by 36.4 percent. Sved et al. (48) applied 16 mg of a 2 percent commercial ointment to the skin of human volunteers. Increasing the surface area from 25 to 100 cm^2, while keeping the dose constant, more than doubled plasma NG concentrations. Blood NG concentrations peaked at 0.15 to 0.18 ng/ml 30 minutes after application to a skin area of 25 cm^2. The NG levels declined rapidly and were undetectable at 90 minutes after application. With an area of 100 cm^2, NG concentrations peaked at levels as high as 0.88 ng/ml at 45 minutes after application; the blood levels declined much more slowly than with the smaller area. When different doses were applied over the same surface area, absorption continued for a substantially longer time as the dose increased (48).

Gross et al. (20) studied dermal absorption by rats of NG from gel and soft paste mixtures. The gel mixture contained 93 percent NG whereas the paste contained 22 percent NG, 6 percent dinitrotoluene, 5 percent trinitrotoluene, 65 percent NaCl, and fillers. A range of concentrations for each preparation was kept in place under a dressing on a shaved area of the back for 4 days for the gel and 8 days for the paste. The rate of absorption, determined from the amount of NG remaining in the dressing, was 0.85 mg/cm^2/hour for the gel and 0.63 mg/cm^2/hour for the paste. Gross et al. concluded that the amount absorbed was dependent on the exposed surface area and, beyond a certain minimal concentration, was independent of the amount applied.

Horhota and Fung (25) examined the influence of the vehicle on the absorption rate of NG applied to the rat abdomen. Absorption was measured by plasma NG levels. Nitroglycerin was absorbed at a much slower rate from applications of pure NG or alcoholic NG solutions than from commercial

ointments containing 2 percent NG in an oleaginous vehicle. There was practically no absorption from gels containing polyethylene glycol.

Other factors which may affect transdermal absorption include differences among individuals, species, and site of application. Substantial individual variation in the rates of percutaneous NG absorption were observed in the rat (20) and in humans (27). Black (4) published plasma concentration curves for seven subjects wearing commercial NG patches (20 cm^2) over a 24-hour period. His data showed that there are extreme fluctuations in NG levels in individual subjects with maxima occurring anywhere between 1 and 20 hours after the start of exposure. A strong interindividual variation in plasma NG levels in human subjects during dermal contact with NG was also observed by Curry (11) and Gjesdal (17). Horhota and Fung (24) studied the influence of the site of dermal contact on NG absorption in rats using plasma NG levels as a measure of the amount absorbed. No plasma NG was observed following application of NG as a 2 percent ointment or as a 6.9 percent alcohol solution to shaved skin on the back; whereas plasma NG levels as high as 30 to 40 ng/ml were achieved following application of the NG ointment to the abdomen. The latter plasma NG levels were maintained throughout the 4-hour exposure period. The differences in absorption from the two anatomical sites apparently were not related to differences in NG metabolism since, in a similar experiment, Yap and Fung (53) found only very low levels of GDN in plasma, as well as no detectable NG, after topical administration to the back skin on the rat.

Horhota and Fung (24) argued that differences in absorption rates from the two anatomical sites were due to differences in the histologic structure of the skin, as the relative depth of cornified tissue is greater in the epidermis on the back than on the abdomen. By applying an NG ointment to an area of the back from which part of the cornified tissue was removed by stripping with adhesive tape, they demonstrated that the stratum corneum may act as a barrier to NG penetration. In this case, NG was present in plasma but the levels were still lower than those observed after application to the abdomen.

Several studies have established that the site of blood collection relative to the site of skin contact can affect the levels of NG detected in the plasma (2, 3, 17). In work with humans, Karim found no NG in blood taken from the contralateral arm when NG was applied to the volar surface of the wrist. However, application of NG to the chest resulted in sustained levels of plasma NG (27). In contrast, Noonan and Wester (41) found no significant differences in the absorption rate from different anatomical sites (chest, inner arm, inner thigh, and postauricular region) in the rhesus monkey. In this study, the absorption rate was measured by the amount of radioactivity excreted in the urine after application of ^{14}C-NG. A possible reason for differences in the results of this study and those of Karim (27) and Horhota and Fung (24) is that the use of urine to assess NG absorption negated the differences in blood plasma levels that can occur when blood is withdrawn from different anatomical sites relative to the site of NG application.

INDUSTRIAL STUDIES

Gjesdal (17) found high plasma NG concentrations among 12 production

workers in a gunpowder plant. Blood samples were collected from the cubital vein before and during work. Plasma NG increased significantly during the work shift. It was not detected in any samples collected before work at 0600 hours but it appeared at 0900 hours and increased between 0900 hours and 1300 hours. Nitroglycerin levels in 0900-hour samples collected on a Tuesday were significantly greater than those in samples collected at the same time on the preceding Monday. However, there was no difference between NG levels collected at 1300 hours on the same 2 consecutive days.

Much higher concentrations of NG were found in the cubital vein than in the femoral vein, indicating that a major part of the NG absorption occurred through the skin of the hands and arms. Absorption through the skin occurred despite the use of protective clothing. Some workers had consistently higher plasma NG levels than others in the same work area. According to Gjesdal, this most likely resulted from individual differences in rates of absorption through the skin rather than rates of NG metabolism since only minimal variations in plasma clearance rates occurred after NG was administered sublingually to the same individuals.

Differences were found in plasma NG concentrations at two different work areas where the airborne NG levels were equal. Thus, there was no association between airborne NG and plasma NG concentrations. The differences in the plasma concentrations at the two sites were attributed to differences in dermal contact with NG. Gjesdal concluded that skin absorption is a major source of plasma NG in the workplace. When the opportunity exists for exposure through both the skin and lungs, the amount absorbed through the lungs would probably be minimal compared to that absorbed through the skin.

Moderate changes in pulse rate and blood pressure occurred during working hours, but these effects were not significantly associated with plasma NG concentrations. In addition, headaches that increased throughout the day were a frequent symptom among workers. However, the occurrence of headaches was not significantly related to NG concentrations in the air or in the blood from the cubital vein (17).

DISCUSSION

Because of its medical implications, most pharmacokinetic studies of transdermal NG absorption focused on plasma NG levels. While few studies addressed urinary metabolites, the available information indicates that NG metabolites are present in urine in sufficiently high concentrations to warrant further consideration of this medium for biological monitoring. As discussed below, there are major information gaps which would necessitate further research before biological monitoring is feasible.

The media most practical for biological monitoring are expired air, urine and blood. Of these, expired air is not suitable for monitoring NG. Although a sizable fraction of the absorbed compound is excreted via the lungs, the NG metabolic product in expired air is CO_2 which, of course, cannot be distinguished from CO_2 derived from other sources.

In 1976, Gotell suggested that plasma levels of ethylene glycol dinitrate (EGDN) and NG could be used to monitor exposure to these compounds in air (19). Gotell measured blood EGDN concentrations in volunteers exposed to known airborne concentrations of the compound (1.2, 6 and 7.8 mg/m^3). Under the conditions of the study, there was no direct dermal contact with EGDN although some airborne material may have been absorbed through the skin. Blood EGDN was highly correlated with airborne EGDN levels in the range 0.9 to 8.0 ng/ml blood. Based on these findings, Gotell suggested that a maximum blood EGDN concentration of 2 ng/ml would correspond to an 8-hour time weighted average exposure (TWA) of 1 mg/m^3. He further estimated that a maximum blood concentration of 4 ng/ml would correspond with an 8-hour TWA for NG exposure of 2 mg/m^3. The maximum blood NG concentration recommended by Gotell seems rather excessive in view of findings that therapeutic topical doses of NG frequently result in NG plasma concentrations in the range of 1 to 10 ng/ml (11).

Although, plasma NG levels may possibly be useful for monitoring exposure to airborne NG, the profile of NG in the blood or urine has questionable potential for use in biological monitoring of skin contact with NG. There is little question that NG becomes elevated in human plasma during extended periods of skin contact. However, NG levels can undergo extreme fluctuations during dermal contact (4, 11) which would make plasma NG an unwise choice for a biological exposure determinant. However, the limited available data do not indicate that NG metabolites undergo such extreme fluctuations (13). Thus, the metabolites may be useful for this purpose.

Only a few studies have examined plasma metabolites during transdermal absorption (13, 39). Dilley found that the levels of metabolites, especially GMN, increased erratically throughout the dermal exposure period, possibly approaching a steady state towards the end of the 5-hour exposure in dogs. Concentrations between 1 to 10 ng/ml and 3 to 20 ng/ml for 1,2-GDN and 1,3-GDN, respectively, were observed. Glyceryl mononitrate levels as high as 100 ng/ml were detected after a 4-hour exposure in one dog. A maximum of 37.5 ng/ml GMN was found in the second dog. (Analyses of total radiolabel in urine suggested that the differences between the two dogs resulted from variances in total absorption rather than rates of metabolism.)

Gjesdal found very high plasma NG levels (2.2 to 44 nmol/l) in dynamite workers (17). Although he did not examine NG metabolites, it can be assumed from studies of NG administered by other routes, that levels of NG metabolites were even higher than those of NG.

These data indicate that detectable levels of metabolites are present in plasma for sufficiently long periods to consider plasma metabolites for use in biological monitoring. If plasma metabolites are used for biological monitoring, then it would be necessary to collect samples towards the end of the work shift because the half-lifes are too short to enable sampling much after exposure has ceased. The available data do not indicate that metabolite levels undergo the intense fluctuations that occur with the parent compound. Unfortunately, insufficient data are available to demonstrate conclusively that plasma metabolite levels are constant enough to use for biological monitoring. Thus, if plasma metabolites were to be considered for this

purpose, studies of changes in plasma concentrations of NG metabolites with time in a number of individuals would be necessary.

Another matter that should be examined further if plasma is to be considered for biological monitoring is the site of blood collection. It is well established that plasma levels of NG vary with the site at which blood is collected relative to the point of dermal contact (2, 3, 17, 27). Whether this problem would be as serious with NG metabolites as with the parent compound is unknown. This phenomenon results, in part, from the extensive metabolism of NG that occurs within the vasculature (2). Since metabolites generated within the vasculature should circulate with a half-life of 30 minutes to 1 hour, they may rapidly reach an equilibrium within the circulatory system and the sampling site may be a lesser problem with metabolites than with the parent compound. If blood were used for biological monitoring, some simple experiments could be performed to confirm this hypothesis.

Because of the ease of collection, urine is the simplest and most efficient fluid for use in biological monitoring. Most studies indicate that up to 50 percent of the NG introduced into the body by various routes is eliminated via the urine where it can be found, primarily in the form of metabolites, for up to 48 hours. Urine should act as a common sink for NG metabolites and should not be affected by factors such as the site of application. If urine were selected for biological monitoring, human studies of the characteristics of metabolites and the time course of their appearance in urine during dermal exposure under controlled conditions would be advisable.

No recommendations can be made concerning which of the NG metabolites would be most useful for biological monitoring until further studies are performed. In making such a decision, it would be advisable to consider the characteristics of the analytical procedures. For example, if plasma GMN were chosen as the biological marker, then it would be necessary to decide whether analytical methodologies would be more amenable to the simultaneous measurement of both isomers or to the measurement of individual isomers. Many analytic procedures for measurement of NG and/or its metabolites in biological materials have been published. This literature should be carefully reviewed to determine the most practical method to use for further studies.

In addition to the work described above, it will be necessary to perform studies designed to establish a biological exposure limit for the chosen determinants. This can be done by examining concentrations of urine or blood metabolites during exposure to a range of NG concentrations and determining the no-observed-effect-level (NOEL) as well as the NG doses that produce minimal physiological effects (i.e., headache, change in blood pressure, or pulse rate).

These criteria would be in accordance with parameters used by NIOSH and the American Conference of Governmental Industrial Hygienist to establish exposure limits for airborne NG (1, 10). An alternative, or confirmatory approach, would be to expose individuals for an extended period of time to airborne concentrations of NG equivalent to the current TLV of 0.05 ppm (1)

and determine levels of metabolites in urine. Ideally, the metabolite concentrations will reflect the total amount absorbed and the same levels could be used as a BEI for transdermal absorption. There are, however, potential problems with this approach (e.g., the extent of NG metabolism within lung tissue may differ from that within the skin, leading to differences in the effects produced by exposure); and it would be less reliable than directly relating urine or plasma concentrations to physiological effects.

Finally, in determining a BEI, the potential effects of repeated NG exposure on NG metabolism and clearance must be considered. The studies of Dilley (13) and Idzu et al. (26) indicate that plasma clearance rates may be longer in animals which experience repeated NG exposure for 7 to 10 days. Thus, the determination of the BEI may best be performed in both nonexposed and experienced NG workers to determine whether important differences exist in the levels that cause physiological effects.

SUMMARY AND RECOMMENDATIONS

In summary, it may be possible to monitor nitroglycerin exposure with NG and/or its metabolites in plasma and urine but further research would be necessary before any of these options could be realized. Urinary NG metabolites represent the best prospect for biological monitoring since urine is easier to collect than plasma, and is not complicated by factors such as the site of collection, which must be considered for blood. Before urine could be used for biological monitoring, human studies of the characteristics of metabolites and the time course of their appearance in urine during dermal exposure under controlled conditions would be necessary. Other studies must be performed to establish a biological exposure limit for the chosen metabolite(s).

REFERENCES

1. American Conference of Governmental Industrial Hygienists. 1986. Committee on Threshold Limit Values: Documentation of Threshold Limit Values, 5th edition.

2. Armstrong, P. W., J. A. Armstrong, and G. S. Marks. 1979. Blood levels after sublingual nitroglycerin. Circulation 59: 585-588.

3. Armstrong, P. W., J. A. Moffat, and G. S. Marks. 1982. Arterial-venous nitroglycerin gradient during intravenous infusion in man. Circulation 66: 1273-1276.

4. Black, C. C. 1982. U.S. Pharmacist (November) 49-75, as cited in Reference 11.

5. Blumenthal, H. P., H. L. Fung, E. F. McNiff, and S. L. Yap. 1977. Plasma nitroglycerin levels after sublingual, oral and topical administration Br. J. Clin. Pharmacol. 4: 241-242.

6. Bogaert, M. G., M. T. Rosseel, and F. M. Belpaire, 1971. Metabolism of nitroglycerin in man: Influence of phenobarbital. Arch. Int. Pharmacodyn. 192: 198-199.

7. Bogaert, M. G., M. T. Rosseel, and A. F. De Schaepdryver. 1969. Excretion in urine of metabolites of glyceryl trinitrate in rabbits. Arch. Int. Pharmacodyn. 179: 480-482.

8. Bogaert, M. G., M. T. Rosseel, and A. F. De Schaepdryver. 1970. Nitroglycerin: Cardiovascular effects and plasma levels in the rabbit. Bruxellas-Medical 50: 567-569.

9. Bogaert, M. G., M. T. Rosseel, and A. F. De Schaepdryver. 1970. The metabolic fate of nitroglycerin in relation to its vascular effects. Eur. J. Pharmacol. 12: 224-230.

10. NIOSH, U.S. Dept. of Health, Education and Welfare, Rockville, MD. 1978. Criteria for a recommended standard. Occupational exposure to nitroglycerin, nitroglycol.

11. Curry, S. H. and S. M. Aburawi. 1985. Analysis, disposition and pharmacokinetics of nitroglycerin. Biopharm. Drug Dispos. 6: 235-280.

12. DiCarlo, F. J., M. C. Crew, L. J. Haynes, M. D. Melgar, and R. L. Gala. 1968. The absorption and biotransformation of glyceryl trinitrate-1-3-14C by rats. Biochem. Pharmacol. 17: 2179-2183.

13. Dilley, J. V. 1977. Evaluation of the occupational health hazards of nitroglycerin using mammalian models, SRI International, Menlo Park, CA, Report No. LSU-5602.

14. Fung, H. L. 1983. Pharmacokinetics of nitroglycerin and long-acting nitrate esters. Am. J. Medicine 13-20.

15. Fung, H. L., S. C. Sutton and A. Kamiya. 1984. Blood vessel uptake and metabolism of organic nitrates in the rat. J. Pharmacol. Exp. Therapeutics 228: 334-342.

16. Givant. Y. and F. G. Sulman. 1978. Experentia 34: 643, as cited in Reference 11.

17. Gjesdal, K. 1985. Exposure to glyceryl trinitrate during gun powder production: plama glyceryl trinitrate concentration, elimination kinetics, and discomfort among production workers. Br. J. Ind. Med. 42: 27-31.

18. Gotell, P. 1971. A method to estimate the total exposure to nitroglycol and nitroglycerin in dynamite workers. Abstracts of the International Cong. of the Permanent Commission and International Association of Occupational Health, Bulgaria, p. 61.

19. Gotell, P. 1976. Environmental and clinical aspects of nitroglycol and nitroglycerin exposure. Occup. Health Saf. 45: 50-51.

20. Gross, E., M. Kiese, and K. Resag. 1960. Absorption of glyceryl trinitrate through the skin. Arch. Toxicol. 18: 331-334.

21. Hodgson, J. R., J. P. Glennon, J. C. Dacre, and C. C. Lee. 1977. Metabolism and disposition of isomers of dinitro- and mononitroglycerol in the rat. Toxicol. Appl. Pharmacol. 40: 65-70.

22. Hodgson, J. R. and C. C. Lee. 1975. Trinitroglycerol metabolism: denitration and glucuronide formation in the rat. Toxicol. Appl. Pharmacol. 34: 449-455.

23. Hogstedt C. and B. Davidsson. 1980. Nitroglycol and nitroglycerin exposure in a dynamite industry, 1958-1878. Am. Ind. Hyg. Assoc. J. 41: 373-375.

24. Horhota, S. T. and H. Fung. 1978. Site dependence for topical absorption of nitroglycerin in rats. J. Pharmaceut. Sci. 67: 1345-1346.

25. Horhota, S. T. and H. Fung. 1979. Percutaneous nitroglycerin absorption in rats. J. Pharmaceut. Sci. 68: 608-612.

26. Idzu, G., Y. Horikoshi, T. Irie, N. Natsume, T. Miyake, Y. Furuta, Y. Wakizaka, H. Abuki, Y. Hashimoto, and M. Ishibashi. 1987. Absorption, distribution, metabolism and excretion of nitroglycerin after nitroglycerin tape (NT-1) administration to rats. Iyakuhin Kenkyu 18: 25-44.

27. Karim, A. 1983. Transdermal absorption of nitroglycerin from microseal drug delivery (MDD) system. Angiology 34: 11-22, from reference 11.

28. Kikukawa, A. and Y. Kagitani. 1985. Blood concentration, excretion and tissue distribution of nitroglycerin [14C(U)] in rats. Yakuri to Chiryo 13: 3921-3929.

29. King, S. P. and H. Fung. 1984. Rapid microbial degradation of organic nitrates in rat excreta. Drub Metab and Disposition 12: 353-357.

30. Langseth-Manrique, K. and J. E. Bredesen. 1986. Simultaneous determination of glyceryl trinitrate and its metabolites in plasma using capillary gas chromatography with on-colummn injection. J. High Res. Chrom. Chrom. Comm. 9: 643-647.

31. Laufen, H. and M. Leitold. 1987. Glyceryl-1-nitrate pharmacokinetics in healthy volunteers. Br. J. Clin. Pharmacol. 23: 287-293.

32. Lee, C. C., H. V. Ellis, J. J. Kowalski, J. R. Hodgson, S. W. Hwang, R. D. Short, J. C. Bhandari, J. L. Sanyer, T. W. Reddig, J. L. Minor, and D. O. Helton. 1976. Mammalian toxicity of munition compounds, Phase II, Effects of multiple doses, Part I, Trinitroglycerin, Progress No. 2, AD AO 47067, Contract No. DAMD17-74-C-4073, Midwest Research Institute, Kansas City, MO.

33. Lloyd, J. F. B. 1986. Glyceryl dinitrates in the detection of skin-contact with explosives and related materials of forensic science interest. Forensic Science Society 26: 341-348.

34. McNiff, E. F., A. Yacobi, F. F. Young-Chang, L. H. Golden, A. Goldfarb, and H. Gung. 1981. Nitroglycerin pharmacokinetics after intravenous infusion in normal subjects. J. Pharmaceut. Sci. 70: 1054-1058.

35. Mizuguchi, S., M. Ishibashi, H. Miyazaki, T. Ezumi, T. Nanbo, T., S. Ohyabu, K. Mitsugi, N. Ishii, and N. Hukasaku. 1982. Distribution and excretion of nitroglycerin in rats. Iyakuhin Kenkyu 13: 848-868.

36. Needleman, P., D. Blehm, A. B. Harkey, E. Johnson, and S. Lang. 1971. The metabolic pathway in the degradation of glyceryl trinitrate. J. Pharmacol. Exp. Therapeutics 179: 347-353.

37. Needleman, P. and F. E. Hunter. 1965. The transformation of glyceryl trinitrate and other nitrates by glutathione-organic nitrate reductase. Mol. Pharmacol 1: 77-86.

38. Needleman, P., S. Lang, and E. Johnson. 1972. Organic nitrates: relationship between biotransformation and rational angina pectoris therapy. J. Pharmacol. Exp. Therapeutics 181: 489-497.

39. Noonan, P. K., and L. Z. Benet. 1987. Variable glyceryl dinitrate formation as a function of route of nitroglycerin administration. Clin. Pharmacol. Therapeut. 42: 273-277.

40. Noonan, P. K. and L. Z. Benet. 1986. The bioavailability of oral nitroglycerin. J. Pharmaceut. Sci. 75: 241-243.

41. Noonan P. K. and R. C. Wester. 1980. Percutaneous absorption of nitroglycerin. J. Pharmaceut. Sci. 69: 365-366.

42. O'Rourke, R. A., V. S. Bishop, P. A. Kot, and J. P. Fernandez. 1971. Hemodynamic effects of nitroglycerin and amyl nitrite in the conscious dog. J. Pharmacol. Exp. Therapeut. 177: 426-432.

43. Reeve, G., T. Bloom, R. Rinsky, and A. Smith. 1983. Cardiovascular disease mortality among nitroglycerin workers. Am. J. Epid. 118: 418.

44. Rosseel, M. T. and M. G. Bogaert. 1973. GLC determination of nitroglycerin and isosorbide dinitrate in human plasma. J. Pharm. Sci. 62: 754-758.

45. Scharpf, F., R. A. Yeates, H. Laufen, and G. Eibel. 1987. Gas chromatographic assay of glyceryl mononitrates in biological samples. J. Chromatog. 413: 91-99.

46. Short, R. D., J. C. Dacre, and C. C. Lee. 1977. A species and developmental comparison of trinitroglycerin metabolism in vitro. Biochem. Pharmacol. 26: 162-163.

47. Soufi, A., F. Pommier, and J. P. DuBois. 1987. Determination of the two dinitrate metabolites of nitroglycerin in human plasma by capillary gas chromatography with electron-capture detection. J. Chromatog. 413: 101-108.

48. Sved, S., W. M. McLean, and I. J. McGilveray. 1981. Influence of the method of application of pharmacokinetics of nitroglycerin from ointment in humans. J. Pharmaceut. Sci. 70: 1368-1369.

49. Svobodova, X., D. Kovacova, V. Ostrovska, A. Pechova, O. Polacikova, S. Kusala, and M. Svobodova. 1988. Determination of nitroglycerin in human plasma using bonded-phase capillary column gas chromatography with electron-capture detection. J. Chromatog. 425: 391-395.

50. Wei, J. Y. and P. R. Reid. 1979. Quantitative determination of trinitroglycerin in human plasma. Circulation 59: 588-592.

51. Woodward, A. J., P. A. Lewis, N. Aykwardm, R. Rudnabm, and J. Maddock. 1984. Determination of nitroglycerin and its dinitrate metabolites in human plasma by high-performance liquid chromatography with thermal energy analyzer detection. J. Pharmaceut. Sci. 73: 1838-1840.

52. Yap, P. S. and H. L. Fung. 1976. Quantitative analysis of nitroglycerin in plasma by gas-liquid chromatography. In Proceedings, APHA Academy of Pharmaceutical Sciences, 6(2), 148.

53. Yap, P. S. and H. Fung. 1978. Pharmacokinetics of nitroglycerin in rats. J. Pharmaceutical Sci. 67: 584-586.

APPENDIX A
APPROVED GLOVES FOR OPERATIONS WITH NG EXPOSURE [a,b]
(approved October 11, 1989)

Area	Operation	Approved type gloves	Minimum change frequency
R.P.	Blender	Leather palm, canvas back, short cuff (41-13-530)	Weekly
		Pylox V-5	Daily
R.P.	Differential Roll, Service Hall, Sheet Cleaning, Rework, Evenspeed (Pad Makeup)	PVC nonventilated (41-13-560)	Weekly
		Leather palm, canvas back, short cuff (41-13-530)	Weekly
R.P.	Evenspeed	Leather palm, long cuff (41-13-520), Men's or 41-13-520, Women's)	Weekly
R.P.	Calender Roll	Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Daily
R.P.	Slitter (Carpet Roll)	Leather palm, canvas back, short cuff (41-13-530)	Weekly
		Cotton, 8 oz. duck, short cuff (41-13-520)	Hourly
		Light cotton, vinyl dipped KSR #22-516, Women's large (41-13-493) or KSR #22-515 Men's Large (41-13-535)	Hourly
R.P.	Carpet Roll and Embossing Roll	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Leather palm, canvas back, short cuff (41-13-530)	Weekly
R.P.	Final Roll	Cotton, 8 oz. duck, long cuff (41-13-490)	Hourly
R.P.	Shear Press	Cotton, 8 oz. duck, long cuff (41-13-490)	Hourly
		Cotton, 8 oz., short cuff (41-13-420)	Hourly
		Light cotton, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515 Men's Large (41-13-535)	Daily
R.P.	Pad Makeup	Pylox V-5 or V-10	Daily

APPENDIX A (cont.)

APPROVED GLOVES FOR OPERATIONS WITH NG EXPOSURE [a,b]

Area	Operation	Approved type gloves	Minimum change frequency
R.P.	Sewing	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Light cotton, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515 Men's Large (41-13-535)	Daily
R.P.	Slitter (Pad)	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Light cotton, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515 Men's Large (41-13-535)	Daily
		Pylox V-5 or V-10	Daily
R.P.	Punch Press	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Daily
		Pylox V-5 or V-10	Daily
R.P.	Magazine Loading	Pylox V-5 or V-10	Daily
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Daily
R.P.	Classifiers	Pylox V-5 or V-10	Daily
R.P.	Sorting	Pylox V-5 or V-10	Daily
R.P.	Shadowgraph	Pylox V-5 or V-10	Daily
R.P.	Nibbler	Pylox V-5 or V-10	Daily
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Daily
R.P.	Cellophane and Inspection	Pylox V-5 or V-10	Daily

APPENDIX A (cont.)

APPROVED GLOVES FOR OPERATIONS WITH NG EXPOSURE [a,b]

Area	Operation	Approved type gloves	Minimum change frequency
R.P.	Packout	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Daily
R.P.	Cleaning Roll, Cleaning Crew	Neoprene rubber, 14" gauntlet Edmont Wilson Neox 9-924 or equivalent	Daily
		PVC nonventilated	Daily
R.P.	LAW Operation, Bearing Pin Insertion, Sorting, Weighing and Packout	Pylox V-5 or V-10	Daily
		Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Daily
R.P.	LAW Operation, Cutting Machine and Sorting	Cotton, 8 oz. duck, long cuff (41-13-490)	Hourly
		Leather palm, canvas back, long cuff (41-13-520)	Weekly
R.P.	Breaker Roll	Leather palm, canvas back, short cuff (41-13-530)	Weekly
C-Line	Mixing, Ingredient Storehouse	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Leather palm, canvas back, short cuff (41-13-530)	Weekly
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Weekly
		Neoprene rubber, 14" gauntlet, Edmont Wilson Neox 9-924 or equivalent	Weekly
		PVC nonventilated (41-13-560)	Weekly

APPENDIX A (cont.)
APPROVED GLOVES FOR OPERATIONS WITH NG EXPOSURE [a,b]

Area	Operation	Approved type gloves	Minimum change frequency
C-Line	20-inch Blocker, Final Blockers, and Finishing Press	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Leather palm, canvas back, short cuff (41-13-530)	Weekly
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Weekly
		PVC nonventilated (41-13-560)	Weekly
C-Line	Handling Solvents and Slurries Preparation	Neoprene rubber, 14" gauntlet, Edmont Wilson Neox 9-924 or equivalent	Weekly
C-Line	Dehydration Press	Neoprene rubber, 14" gauntlet	Daily
C-Line	Cutting Machine and Traying	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Weekly
		Pylox V-5 or V-10	Daily
Cast	Mold Assembly, Mold Loading	Cotton, 8 oz. duck, short cuff (41-13-420)	Hourly
		Leather palm, canvas back, short cuff (41-13-530)	Weekly
Cast	Casting, Mold Disassembly, Mold Parts Washing, Desiccator Cleaning	Leather palm, canvas back, short cuff (41-13-530)	Weekly
		PVC nonventilated (41-13-560)	Daily
		Neoprene rubber, 14" gauntlet, Edmont Wilson Neox 9-924 or equivalent	Daily
Cast	Handling Carpet Rolls, Uninhibited Grains and Stick Propellant (DRAGON, TOW Launch, M-26 or M-30)	Neoprene rubber, 14" gauntlet, Edmont Wilson Neox 9-924 or equivalent	Daily
		PVC nonventilated (41-13-560)	Daily
		Leather palm, canvas back, short cuff (41-13-530)	Weekly
		Pylox V-5 or V-10	Daily

APPENDIX A (cont.)

APPROVED GLOVES FOR OPERATIONS WITH NG EXPOSURE [a,b]

Area	Operation	Approved type gloves	Minimum change frequency
Cast	Inhibiting (End Sleeving and End Inhibiting)	Pylox V-5 or V-10	Daily
		Natural latex, white surgical, Edmont Wilson #46-320 or equivalent (41-13-495)	Daily
Cast	Handling Inhibited Grains	Neoprene rubber, 14" gauntlet, Edmont Wilson Neox 9-924 or equivalent	Daily
		PVC nonventilated (41-13-560)	Daily
		Leather palm, canvas back, short cuff (41-13-530)	Weekly
		Pylox V-5 or V-10	Daily
		Natural latex, white surgical, Edmont Wilson #46-320 or equivalent (41-13-495)	Daily
		Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Weekly
Cast	Cutting Machine	Light cotton knit, vinyl dipped KSR #22-513, Women's Medium (41-13-493) or KSR #22-515, Men's Large (41-13-535)	Weekly
		Pylox V-5 or V-10	Daily
		Natural latex, white surgical, Edmont Wilson #46-320 or equivalent (41-13-495)	Daily
Pilot B	Washing FAD Doors and Washing Trays	Neoprene rubber, 14" gauntlet, Edmont Wilson Neox 9-924 or equivalent	Daily
		PVC nonventilated (41-13-560)	Daily
Pilot B	Cabinet Handling	Leather palm, canvas back, short cuff (41-13-530)	Weekly

a. All cleanup operations (Oakite, Arctic-Syntex-M-Beads, NG remover, acetic acid, and other solvents) shall require the use of the Neoprene rubber, 14" gauntlet, Edmont Wilson Neox 9-24 or equivalent (41-13-590) or the PVC nonventilated glove (41-13-560).
b. R.P. = Rolled Powder, LAW = Light Antitank Weapon, TOW = Tube-launched, Optically-tracked, Wire-guided missile, FAD = Forced Air Dryer.

APPENDIX B

GLOSSARY OF TERMS

ASTM	American Society for Testing and Materials
BEI	biological exposure index
DEGDN	diethyleneglycol dinitrate
FAD	forced air dryer
GC/ECD	gas chromatography (with) electron capture detection
GDN	glyceryl dinitrate
GMN	glyceryl mononitrate
INAAP	Indiana Army Ammunition Plant
LAW	light antitank weapon
NG	nitroglycerin (glyceryl trinitrate)
NIOSH	National Institute for Occupational Safety and Health
NOEL	no observed effect level
RAAP	Radford Army Ammunition Plant
R.P.	rolled powder
TOW	tube-launched, optically-tracked, wire-guided (missle)
TWA	time-weighted average
USAMCCOM	U.S. Army Armament, Munitions and Chemical Command
USAMRDC	U.S. Army Medical Research and Development Command
V_d	volume of distribution

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